REMARKS

The Claimed Invention

The claimed invention is directed to methods for making antibodies to a host chaperone protein and conformers thereof.

The Pending Claims

Prior to entry of the above amendments, Claims 12-14 and 51-53 are pending.

The Office Action

Claims 12-14 and 51-53 stand rejected under 35 USC § 112, first paragraph, written description and enablement.

Claims 12-14 and 51-53 stand rejected under 35 USC § 112, second paragraph

Claim 13 stands rejected under 35 USC § 102.

Claims 13-14 stand rejected under 35 USC § 103(a).

Amendments

New claim 54 has been added. Support for new Claim 54 can be found, for example, in paragraph 0051.

No new matter is introduced by the amendments and the Examiner is respectfully requested to enter them .

Response to the objections and rejections

In the response that follows, the Examiner's individual rejections are provided in full text, as identified by indented small bold print, followed by Applicant's response.

Specification

Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification.

The disclosure is objected to because of the following informalities: Example 12 is found on page 42 and on page 45, it appears that the example on page 45 should be number 13.

Appropriate correction is required.

The above information has been corrected.

35 U.S.C. 112 (2nd paragraph) Rejection

The rejection of claims 12-14 and 51-53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the reasons of record.

Applicant's arguments have been fully considered but fail to persuade. Applicant's arguments are that the term refers to a protein which exists in two or more tertiary structures which also exhibit different function. Applicant makes reference to figure 14 as evidencing that there are two different conformational structures that are associated with HSP68. The experiment uses an immunoprecipitation procedure in which a polyclonal antibody against HuHP68 was used to precipitate the HP68 complexes. Cells transfected with plasmid carrying Gag or BruΔenv were subjected to immunoprecipitation. The result that only Gag was precipitated HP68 was interpreted by Applicant's to mean that there are two conformational structures "conformers" for HP68. This interpretation is not convincing because (1) the HP68 may have a higher affinity for Gag and therefore the cellular pool of HP68 will associated with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to produce the RNase L inhibitor which then binds to RNase L displacing HP68 from the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates with Gag or RNase L [see Martinand et al. RNalse L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 25A?RNase L pathway in human T cells. Journal of Virology (Jan. 1999) Vol. 73, No. 1, pages 290-296; or Bisbal et al. Cloning and characterization of RNase L inhibitor. Journal of Biological Chemistry (1995) Vol. 270, No. 22, pages 13308-13317]. Therefore, term "conformer" renders the claims indefinite because the ordinary artisan would not know what is meant by this term.

Applicants respectfully traverse the rejection of Claims 12-14 because the evidence provided in the specification does support the existence of at least two tertiary structures of the amino acid sequence shown in SEQ. ID. No: 6.

In the response filed October 2, 2003, Applicants drew the Examiner's attention to Figure 14 which shows that one of those tertiary structures, HP68 protein, facilitates HIV-1 capsid formation and binds to HIV-1 Gag and Vif proteins. However, HP68 does not bind to RNase L in human cells, which have been transfected with plasmids expressing Gag alone or with the plasmid pBRUΔenv (*see* page 49, lines 1-17). A protein having the amino acid sequence shown

in SEQ. ID. No: 6 is known to associate with and inhibits RNase L. These findings suggest that there are two different tertiary structures of SEQ. ID. No: 6 that not only act by two different mechanisms but in addition reside in two different complexes in host cells.

The Examiner asserts that the data provided by Applicants concluding that HP68 is a different tertiary form of SEQ. ID. No: 6 from the protein with the same amino acid sequence that is known to bind to RNaseL, HuHP68, are not convincing because "(1) the HP68 may have a higher affinity for Gag and therefore the cellular pool of HP68 will associate with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to produce the RNase L inhibitor which then binds to RNase L displacing HP68 from the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates with Gag or RNase L" (Official action mailed August 2, 2004, page 3).

These scenarios posed by the Examiner are inapt because Applicants' data are generated using cell free systems, therefore there is no cellular pool of HP68. Applicants respectfully refer the Examiner to the data that are presented in Figures 10 and 11. If HP68 binds to Gag but does not bind to RNaseL, then it must be different in some way from the protein having substantially the same amino acid structure that does bind to RNaseL. Cos-1 cells expressing pBRUΔenv were immunoprecipitated using αHuHP68b followed by immunoblotting with antibodies to Gag, Vif, Nef, RNase L and actin. αHuHP68b co-immunoprecipitated Gag and Vif under native conditions but not denatured conditions. RNase L and HIV Nef protein were not co-immunoprecipitated. Also *see* also the text beginning on page 48 entitled "6. HP68 selectively associates with HIV-1 Gag and Vif but not with RNase L" and figure 14.

The specification has not provided a way to distinguish between the "conformers". Does "conformer" refer to the immature capsid in association with HP68 or does conformer refer to a mutant of HP68. The phrase "conformer" renders the claims indefinite because the specification does not provide a standard of measuring the degree intended by the term, thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(f).

Several methods for detecting a conformational difference between proteins are provided. Beginning at paragraph 0044 and continuing through paragraph 0046, various methods are

described. Also *see* paragraph 0054 and 0055. The term "conformer" is defined in paragraph 0027. It does not refer to the immature capsid in association with HP68, nor does it refer to a mutant of HP68. Rather, it refers to the relationship between two proteins, much the same way that the term "isozyme" does or that the term "isomers" refers to the relationship between two chemicals.

35 U.S.C. 112 (1st paragraph) Rejection

The rejection of claims 12-14 and 51-53 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reason of record.

Applicant's arguments have been fully considered but fail to persuade. Applicant's argument is that the methods of making a knock out mouse are well established in the art citing several references.

Neither the specification nor the prior art has provided any teaching regarding such a knockout animal, i.e. a mouse with a homozygous disruption of the gene encoding HP68. The specification has not disclosed any monoclonal antibodies produced by the methods as claimed. All transgenic models, whether targeted or untargeted, still may present unpredictable expression patterns due to incomplete knockout of the targeted gene, redundancy within the genome or unanticipated genetic interactions, such as down-regulation of other genes. (Taconic Newsletter, March 1996, Vol. 1, No. 2, page 4).

The claims encompass a genus of compounds (monoclonal antibodies) defined only by their function "binding to a conformer" without disclosing the structural differences between the "conformers". Applicant makes reference to figure 14 as evidencing that there are two different conformational structures that are associated with HSP68. The experiment uses an immunoprecipitation procedure in which a polyclonal antibody against HuHP68 was used to precipitate the HP68 complexes. Cells transfected with plasmid carrying Gag or BruΔenv were subjected to immunoprecipitation. The result that only Gag was precipitated HP68 was interpreted by Applicant's to mean that there are two conformational structures "conformers" for HP68. This interpretation is not convincing because (1) the HP68 may have a higher affinity for Gag and therefore the cellular pool of HP68 will associated with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to produce the RNase L inhibitor which then binds to RNase L displacing HP68 from the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates with Gag or RNase L [see Martinand et al. RNalse L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 25A?RNase L pathway in human T cells. Journal of Virology (Jan. 1999) Vol. 73, No. 1, pages 290-296; or Bisbal et al. Cloning and characterization of RNase L inhibitor. Journal of Biological Chemistry

(1995) Vol. 270, No. 22, pages 13308-13317]. The fact that one could have assayed/screened for a compound of interest using does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. In order to measure binding to a particular conformation structure would require that this tertiary structure is stable. Without such stability it would require undue experimentation (be an undue burden) to randomply screen undefined compounds for the claimed activity of binding a "conformer".

Claimed invention is drawn to an antibody identified by the method of claim 12. However, no structural or specific functional characteristics (specific epitope binding) of such an antibody is provided, nor is there any indication that the artisan actually implemented the method of claim 12 so as to identify any monoclonal antibodies. This situation is analagous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *Vas-Cath-Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". (See page 1117) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see *Vas-Cath* at page 1116.) Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention. The claim fails to comply with the written description requirement.

Applicants respectfully traverse this rejection because the rejected Claims are original Claims in the application as filed, and therefore, by definition Applicants were in possession of the claimed subject matter at the time application was filed. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

The rejection of claims 12-14 and 51-53 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record.

Applicant's arguments have been fully considered but fail to persuade. Applicant's arguments are (1) that the methods of making a knock out mouse are well established in the art and (2) that the structure of the monoclonal antibody is not important per se but rather the three dimensional structure of the protein "conformer" used to generate the monoclonal antibody is significant.

Neither the specification nor the prior art has provided any teaching regarding a HP68 knockout animal. The specification also has not disclosed any monoclonal antibodies produced by the claimed method. All transgenic models, whether targeted or untargeted, still may present unpredictable expression patterns due to incomplete knockout of the targeted gene, redundancy within the genome or unanticipated genetic interaction, such as down-regulation of other genes. (Taconic

Newsletter, March 1996, Vol. 1, No. 2, page 4). Indicating that until an animal has actually been created there is a high degree of uncertainty. The claims as written do not appear to require germline transmission of the disrupted nucleotide sequence. It would be unpredictable if a disruption of a nucleotide sequence in a single cell would result in a phenotype (that would not have any HP68 protein in the animal); the instant specification has not provided any uses for a transgenic mouse that does not exhibit a phenotype resulting from disruption of a nucleotide sequence (see below). The claims encompasses transgenic mice that comprise a disruption in a host chaperone protein encoding gene, particularly the nucleotide sequence of HP68. Claims 12 embrace transgenic mice exhibiting a particular phenotype, whereing a broad interpretation of the claimed animals could read on disruption of a host chaperone protein encoding gene in a single cell. The specification has not taught that transgenic mouse embryos whose genomes comprise a homozygous disruption of the HP68 encoding gene and that these animals do not exhibit a phenotype of embryonic lethality. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al. Gene targeting in embryonic stem cells: the new physiology and metabolism. Journal of Molecular Medicine (1997) Vol. 75, pages 208-216; see pate 208, column 2, last full paragraph). Also see Leonard et al (Role of the common sytokine receptor gamma chain in cytokine signaling and lymphoid development. Immunological Reviews. (1995) No. 148, pages 97-114) who discusses that inactivation of the gene encoding cytokine receptor chain in transgenic mice results in a phenotype different from that expected. Finally, Moens et al. (Defects in heart and lung development in compound heterozygotes for two different targeted mutations at the N-myclocus. Development (1993) Vol. 119, pages 485-499) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). However, it would be difficult to predict any phenotype resulting from disruption of the sequence encoding HP68 in light of the above. Moreover, as the claims read on disruption of a host chaperone protein (HP68) protein encoding gene in a single cell, it would be unpredictable if such a disruption would result in any phenotype. The specification has not disclosed a transgenic mouse embryos whose genome comprises a homozygous disruption in the nucleotide sequence encoding the HP68 gene does not display embryonic lethality. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

The claims encompass a genus of compounds (monoclonal antibodies) defined only by the function "binding to a conformer" without disclosing the structural differences between the "conformers". Applicant makes reference to figure 14 as evidencing that there are two different conformational structures that are associated with HSP68. The experiment uses an immunoprecipitation procedure in which a polyclonal antibody against HuHP68 was used to precipitate the HP68 complexes. Cells transfected with plasmid carrying Gag or BruΔenv were subjected to immunoprecipitation. The result that only Gag was precipitated HP68 was interpreted by Applicant's to mean that there are two conformational structures "conformers" for HP68. This interpretation is not convincing because (1) the HP68 may have a higher affinity for Gag and therefore the cellular pool

of HP68 will associated with Gag when present in the cell (2) or alternatively that the presence of a plasmid or Gag in the cell may stimulate the cell to produce the RNase L inhibitor which then binds to RNase L which will then displace HP68 from the RNase L. Either scenario does not indicate that there are structural differences between HP68 when it associates tithe Gag or RNase L [see Martinand et al. RNalse L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 25A?RNase L pathway in human T cells. Journal of Virology (Jan. 1999) Vol. 73, No. 1, pages 290-296; or Bisbal et al. Cloning and characterization of RNase L inhibitor. Journal of Biological Chemistry (1995) Vol. 270, No. 22, pages 13308-13317].

Making antibodies to a conformational structure is not a trivial matter and requires more than a mere road map on how applicants envision the production of this antibody. The generic procedure of immunizing a homozygous knockout animal with a protein having a stable conformational structure does not predictably result in an antibody that can recognize one "conformer" over the other "conformer" (see Prusiner et al. Ablation of the prion protein (PrP) gene in mice prevents scrapie and facilitates production of anti-PrP antibodies. Proceeding of the National Academy of Science (1993) Vol. 90, pages 10608-10612;). The lack of PrPC in PrPp0/0 mice prevents them from becoming tolerant to the immunogen, the injection of the PrPSc infectious structure into the animal produced antibodies against PrP but these antibodies did not distinguish between the prion "conformers". "Surprisingly, given that we immunized mice with infectious Prp27-30 preparation, none of the rescued antibodies exclusively recognized this form of protein, whereas all but one antibody reacted well with a PrPC as it occurs on the cell surface" (see Williamson et al. Mapping the prion protein using recombinant antibodies. Journal of Virology (1998) Vol. 72, No. 11, pages 9413-9418, page 9417, collum 1, 2nd paragraph).

The fact that one could have assayed/screened for a compound of interest using the claimed does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. In order to measure binding to a particular conformation structure it would require that this tertiary structure is stable. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. The instant fact pattern fails to disclose that a monoclonal antibody has been produced using the claimed knockout animal. The specification does not provide any guidance or any working examples in this unpredictable art, and thus the artisan would have been unable to have prepared the claimed antibody without undue experimentation. Furthermore an assay for finding a product is not equivalent to a positive recitation of how to make such a product. This claim fails to meet the enablement requirement for the "how to make" prong of 35 U.S.C. § 112 first paragraph.

Applicants have avoided this rejection by amendment of the claims to add new Claim 54 which describes the specific steps of preparing a knockout mouse and amending Claim 12 to depend from Claim 54. Also, applicants note that the conformers are

obtained using a cell free system , and therefore there is no cellular pool of HP68. The knowhow for obtaining knock out animals is well known to those of skill in the art. Furthermore, the number of proteins to which antibodies are made is small. As applicants have shown, there are five intermediates in the pathway of HIV capsid assembly. Therefore , the maximum universe of chaperone proteins is five and it does not constitute undue experimentation to produce monoclonal antibodie sto these chaperone proteins. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. 102 Rejection

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by >Willison et. Al (Cell, 1989) as evidenced by applicants specification page 45 lines 25-27 indicating that the 23c antibody was used for the isolation of the WG68 conformer.

The instant invention is drawn to a monoclonal antibody that binds HP68. The recitation "conformational specificity for host chaperone protein that is involved in assembly of immature HIV capsid and not to conformers of said host chaperone protein that do not bind Gag and do not facilitate HIV capsid assembly". has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F2d 67, 190 USPQ 15(CCPA 1976) and *Kropa v. Robie*, 187 F2d 150, 152, 88 USPG 478, 481 (CCPA 1951).

Willison et al. discloses the production of a 23c hybridoma cell line producing a monoclonal anti-TCP-1alpha antibody, now available for purchase from Stressgen Biotechnologies (see table 1). This antibody was used by Applicant's to isolate the HP68 from wheat germ extracts, indicating that a known antibody structure binds HP68. Therefore, the instant invention drawn to monoclonal antibodies is anticipated by Willison et al.

This rejection is avoided by amendment of the claims to move the language relating to the specificity of antibody from the preamble to the body of claim. An antibody having such specificity is not taught by Willison et al. Accordingly, the Examiner is respectfully requested to withdraw this rejection

35 U.S.C. 103 Rejection

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13 and 14 are rejected under 35 U.S>C. 103(a) as being obvious over Willison et. Al (Cell, 1989) as evidenced by applicants.

The instant invention is drawn to a monoclonal antibody that binds HP68. The recitation "conformational specificity for host chaperone protein that is involved in assembly of immature HIV capsid and not to conformers of said host chaperone protein that do not bind Gag and do not facilitate HIV capsid assembly" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim foes not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Willison et al teaches the production of a 23c hybridoma cell line producing a monoclonal anti-TCP-1alpha antibody, now available for purchase from Stressgen Biotechnologies (see table 1). This antibody was used by Applicant's to isolate the HP68 from wheat germ extracts, indicating that a known antibody structure binds HP68. The reference does not teach making antibody-binding fragments. The production of antibody-binding fragments from an intact antibody is a well-known art established technique. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody-binding fragments from an intact antibody. One having ordinary skill in the art would habe had a high expectation of success in making such fragments form an intact antibody. Therefore, the instant invnetion is obvious over the cited references disclosing the 23c antibody.

This rejection is avoided by amendment of the claims to move the language relating to the specificity of antibody from the preamble to the body of claim. As noted above, an antibody having such specificity is not taught by Willison et al. Accordingly, the Examiner is respectfully requested to withdraw this rejection

35 U.S.C. 112 Rejection

Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is

apparent specific antibody is required to practice the claimed invention. The specification page 45 lines 25-27 indicates that the 23c antibody was used for the isolation of the WG68 conformer. As such they must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise known and readily available to the public. In the instant case the specification has set out a method of making antibodies, yet the only antibody discloaed is the 23c antibody. If it is not so obtainable or available, the requirements of 35 U.S.C. 112, first paragraph, may be satisfied by an enabling deposit of the cell line producing the antibody. Therefore, a deposit at a recognized depository may be made for enablement purposes.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

© the deposit will be maintained in a public depository for a period of 30 years. Or 5 years after the last request for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

This rejection is respectfully traversed because methods of making knockout mice and antibodies are well known to those of skill in the art. Furthermore, the applicants are provided peptide sequences for use as immunogens , as well as methods for making the HP68 conformer in a cell free system. Since the claimed invention is adequately described applicants respectfully submit that no deposit is required. Accordingly, the examiner's respectfully requested to withdraw this rejection.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (831) 648-3090.

Respectfully submitted,

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